

REMARKS

Applicant respectfully requests reconsideration of the present Application as amended. Claims 1-29 were pending in the application, with claims 3-4, 6, 9-11, 14-16, 19, and 23-25 being withdrawn from consideration by the Examiner. By the present Amendment, claims 3-4, 6, 11, 13-16, 19-20, 23-25, 27, and 29 have been cancelled, claim 1 has been amended as discussed below, and claims 5, 9, 26 and 28 have been amended for form. New claims 30-45 have been added and are supported by the specification as filed. No new matter has been added to this application by this amendment. Each of the rejections levied by the Examiner is addressed in turn below.

Rejection of Claims 1-2, 5, 7-8, 11, 13, 17-18, 20-21, and 26-27 under 35 U.S.C. § 103

Claims 1-2, 5, 7-8, 11, 13, 17-18, 20-21, and 26-27 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over U.S. Patent 7,060,299 (hereinafter, "Alavattam"), in view of Norris *et al.*, *J. Apply. Poly. Sci.*, 63:1481-1492 (1997) (hereinafter, "Norris") and in view of U.S. Patent No. 7,157,426 (hereinafter, "Quay").

Without conceding the correctness of the Examiner's rejection and solely to expedite prosecution, claim 20 has been cancelled, and claim 1 has been amended to recite that the surface-altering agent reduces the overall charge on the surface of the polymeric particle and enhances the hydrophilicity of the surface of the polymeric particle compared to the same particle except without a surface-altering agent disposed on the surface, that the surface-altering agent comprises polyethylene having a molecular weight of about 2-3 kDa (referred to herein as "PEG_{2-3K}"), and that the polymeric particle is less than about 1 micron in diameter. Neither Alavattam, Norris, Quay, nor any combination of these references teaches or renders obvious all of these claimed features.

Specifically, neither Alavattam, Norris, nor Quay teaches the use of PEG_{2-3K}. Thus, even if one of ordinary skill in the art combined the teachings of Alavattam, Norris, and Quay in the manner suggested by the Examiner, all of the features of claim 1 would still not be described. Thus, claim 1 and the claims that depend therefrom are not obvious in view of this combination of references for at least this reason.

Moreover, for the reasons below, Applicant believes that disposing PEG_{2-3K} on the surface of a particle to enhance its mobility in mucus is a surprising result that would not have been expected at the time of the invention. The inventors have discovered that modification of particles

with PEG_{2-3K} disposed on the surface of the particles enhances the average rate at which the particles move in mucus by at least 5-fold compared to the same particles except without a surface-altering agent disposed on the surface. This result is described in at least paragraphs [0214] – [0224] of the publication of the present application (US2008/0166414). The use of PEG_{2-3K} to enhance particle mobility in mucus is a surprising and unexpected result, as PEG was generally thought to be *mucoadhesive* (*i.e.*, resulting in poor mobility in mucus) before the present invention.

The notion that PEG was generally thought to have poor mobility in mucus is supported by Norris. Norris teaches different values of translocation permeability (P_T) for microspheres (MS) functionalized with different functional groups (*e.g.*, amidine, carboxyl, carboxylate, and sulfate). Figure 8 of Norris shows that microspheres functionalized with different functional groups had a translocation permeability ranging from 2.63×10^{-5} cm/min to 5.36×10^{-4} cm/min, with the PS-amidine microsphere having the greatest translocation permeability. Nowhere does Norris teach or suggest modifying a microsphere with a polymeric coating, especially PEG. Norris teaches, however, that particles of PEG-4000 (that is, PEG having a molecular weight of 4 kDa), have a translocation permeability in intestinal mucosa of 8.58×10^{-5} cm/min. Norris teaches that this rate of transport in mucus for PEG-4000 was an order of magnitude *less* than that for microspheres functionalized with different functional groups; see, for example, page 1490, right column, which states that “The P_T [for PS-CML] was estimated to be 7.94×10^{-4} cm/min, which is 10 times greater than the P_T observed for PEG-4000 through intestinal mucosa.” Therefore, Norris does not support the use of PEG for enhancing the mobility of particles in mucus.

Several publications enclosed herewith that pre-date the invention teach that PEG was generally thought to be mucoadhesive. See, for example, page 66, right column of Huang *et al.*, “Molecular aspects of muco- and bioadhesion: Tethered structures and site-specific surfaces,” *J. Controlled Release*, 65 (2000), 63-71¹, which states “we found that if we incorporated free PEG chains in the particles, mucoadhesion was improved significantly because of the penetration of the free PEG chains across the mucosa-polymer interface.” See also the abstract of Peppas *et al.*,

¹ This reference is being cited in an IDS filed herewith.

“Poly(ethylene glycol)-containing hydrogels in drug delivery”, *J. Controlled Release*, 62 (1999), 81-87², which states that a number of hydrogel carriers such as PEG are mucoadhesive.

These teachings in Norris, as well as the general teachings in the art prior to the invention, suggest that even if one of ordinary skill in the art had thought of modifying the surface of a particle with a polymer in order to increase transport in mucus (which Applicant believes would not have been the case based on the teachings in Norris, Alavattam, and Quay), he or she would *not* have contemplated using PEG_{2-3K} specifically because it was generally believed that PEG was mucoadhesive and would have had led to lower mobility in mucus.

The Examiner also states that one of ordinary skill in the art would have combined the particles of Alavattam with the surfactants disclosed in Quay in order to increase particle transport in mucus. It is noted that Quay is focused on enhanced delivery across hydrophobic *mucosal membranes*, and not enhanced delivery across *mucus* as presently claimed. Mucus is a viscoelastic gel (the primary component being high molecular weight mucin glycoproteins), whereas the mucosal membrane is formed primarily of lipids. The chemical and physical makeup of mucus is very different from that of a mucus membrane, and therefore, the transport characteristics across each of the substances are also very different. Quay recognizes the differences between transport across a mucosal membrane and transport across mucus in column 26, line 59, to column 28, line 4, and teaches that mucolytics and mucus-clearing agents (for addressing the issue of transport across mucus) can optionally be used in combination with the methods of the Quay invention (directed towards transport across mucosal membranes). The rejections in the Office Action regarding the teachings in Quay relate to substances that may increase transport across *mucosal membranes*; thus, one of ordinary skill in the art would not have combined such substances with the particles of Alavattam for increasing transport of particles *in mucus* as claimed. It is further noted that although Quay teaches certain materials that may be used as mucolytic and mucus-clearing agents, none of these agents include PEG, especially PEG_{2-3K} as claimed.

For at least these reasons, the asserted combination of Alavattam in view of Norris and Quay does not render independent claim 1 obvious. The remaining claims rejected on this ground depend

² This reference is being cited in an IDS filed herewith.

directly or indirectly from independent claim 1, and, therefore, are patentable over the asserted combination of Alavattam in view of Norris and Quay for at least these same reasons.

Claims 1 and 12 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Alavattam, in view of Norris and Quay, and further in view of Singh *et al.*, *PNAS*, 97(2):811-816, 2000 (hereinafter, “Singh”). As described above, the asserted combination of Alavattam in view of Norris and Quay does not render claim 1 obvious. Singh does not cure the deficiencies in the combination of Alavattam in view of Norris and Quay. Therefore, claim 1, and claim 12 which depends therefrom, are patentable in view of the asserted combination of Alavattam in view of Norris and Quay and further in view of Singh.

Claims 1 and 22 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Alavattam, in view of Norris and Quay, and further in view of U.S. Patent 5,612,053 (hereinafter, “Baichwal”). As described above, the asserted combination of Alavattam in view of Norris and Quay does not render claim 1 obvious. Baichwal does not cure the deficiencies in the combination of Alavattam in view of Norris and Quay. Therefore, claim 1, and claim 22 which depends therefrom, are patentable in view of the asserted combination of Alavattam in view of Norris and Quay and further in view of Baichwal.

Claims 1 and 28-29 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Alavattam, in view of Norris and Quay, and further in view of Dawson *et al.*, *Vet. Rec.* 127(13):338, 1990 (hereinafter “Dawson”). As described above, the asserted combination of Alavattam in view of Norris and Quay does not render claim 1 obvious. Dawson does not cure the deficiencies in the combination of Alavattam in view of Norris and Quay. Therefore, claim 1, and dependent claim 28, are patentable in view of the asserted combination of Alavattam in view of Norris and Quay and further in view of Dawson.

Claim 29 has been cancelled, rendering the rejection of this claim moot.

Accordingly, withdrawal of the rejections under § 103 is respectfully requested.

CONCLUSION

The Examiner may address any questions raised by this submission to the undersigned at 617-951-7000. Applicants believe we have appropriately provided for fees due with this response. However, if there are any other fees due in connection with filing this submission, please charge our Deposit Account No. 18-1945, under Order No. JHUC-P01-021 from which the undersigned is authorized to draw.

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Respectfully submitted,

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